

Chapter 43: Sepsis and Septic Shock

INTRODUCTION

- Sepsis-3 redefined sepsis by combining sepsis and severe sepsis from the Sepsis-2 guideline.
- All-cause mortality in sepsis is 10%–20%, and the mortality rates increase proportionally with severity, approaching 40% or greater in septic shock.

ETIOLOGY

- Patients at risk of infection who are predisposed to sepsis include advanced or very young age; chronic conditions including heart failure, diabetes, chronic obstructive pulmonary disease, cirrhosis, [alcohol](#) dependence, and end-stage renal disease; and other immunosuppressive diseases such as neoplasm and human immunodeficiency virus (HIV) disease.
- The most common anatomic source of infection that leads to sepsis is the lung (40%–42%), followed by intra-abdominal space (31%–34%) and genitourinary tract (11%–15%). The microorganisms isolated from blood cultures of patients with sepsis or septic shock include gram-negative organisms in 44%–59% of patients, gram-positive bacteria in 37%–52%, anaerobic organisms in 5%, and fungi in 4%–10%.
- *Escherichia coli* is by far the most commonly isolated gram-negative microorganism in sepsis (25%–34%), followed by *Klebsiella* species, *Proteus* species, *Enterobacter* species, and *Pseudomonas aeruginosa*. Mortality increases significantly with increasing severity of sepsis (3.5% for sepsis, 9.9% in severe sepsis, and 29% in septic shock), especially in presence of *P. aeruginosa*. The most common gram-positive organisms are *Staphylococcus aureus*, followed by *Streptococcus* and *Enterococcus*.
- *Candida* species (particularly *Candida albicans*) are common fungal etiologic agents of bloodstream infections.
- Septic shock is the most ominous complication associated with gram-negative sepsis. Another complication is sepsis-associated disseminated intravascular coagulation (SA-DIC). Simultaneous widespread microvascular thrombosis and profuse bleeding from various sites characterize SA-DIC. SA-DIC can produce acute renal failure, hemorrhagic necrosis of the gastrointestinal (GI) mucosa, liver failure, acute pancreatitis, acute respiratory distress syndrome (ARDS), and pulmonary failure.
- ARDS and sepsis-associated acute kidney injury are other common complications of sepsis. ARDS can result in loss of functional alveolar volume, impaired pulmonary compliance, and profound hypoxemia.
- The hallmark of the hemodynamic effect of sepsis is the hyperdynamic state characterized by low systemic vascular resistance and high cardiac output with tachycardia and arterial hypotension.

CLINICAL PRESENTATION

- Symptoms of sepsis are usually nonspecific and include fever, chills, constitutional symptoms of fatigue, general malaise or myalgia, and changes in mental status ([Table 43-1](#)).
- The clinical presentation of sepsis varies significantly depending on the site of the infection (ie, pulmonary versus urinary tract) and host response to the infection based on the patient's underlying health status and risk factors. The initial presentations may include general malaise or myalgia and nonspecific signs such as fever (or hypothermia), chills, tachycardia, tachypnea, or change in mental status.
- Arterial hypotension may compromise organ perfusion, leading to oliguria. Hyperventilation may cause impaired gas exchange, which can lead to



respiratory alkalosis. Altered glucose metabolism, including impaired gluconeogenesis and excessive insulin release, is evidenced by either hyperglycemia or hypoglycemia. Increased glycolysis with impaired clearance of **lactate** by the hypoperfused liver and kidneys results in elevated **lactate** levels, which then contribute to metabolic acidosis.

- Organ dysfunction can be evaluated by using the Sequential Organ Failure Assessment (SOFA) scoring system, which includes assessment of pulmonary, coagulation, hepatic, cardiovascular, renal, and neurological systems and gives a score ranging from 0 to 4 for each system. A higher total score is associated with an increased probability of mortality, and an increase in SOFA score of 2 or more increases mortality by 10% in hospitalized patients with presumed infection

TABLE 43-1

Clinical Findings of Sepsis

Clinical Signs and Symptoms	Laboratory Signs
Fever or hypothermia (temp >38.3°C [100.9°F] or <37°C [98.6°F])	Leukocytosis, leukopenia (WBC >12,000/μL [$12 \times 10^9/L$], <4,000/μL [$4 \times 10^9/L$])
Rigors, chills	Hyperlactatemia (>2 mmol/L [18 mg/dL])
Myalgias, malaise, lethargy	Serum creatinine increase >0.5 mg/dL (44 μmol/L)
Altered mental status	Acute oliguria (urine output <0.5 mL/kg/h)
Nausea, vomiting	Thrombocytopenia (platelet <100,000/μL [$100 \times 10^9/L$])
Tachycardia (HR >90 beats/min)	INR >1.5 or aPTT >60 seconds
Tachypnea (RR >20 breaths/min)	Hyperglycemia (plasma glucose >140 mg/dL [7.8 mmol/L])
Hypotension systolic BP <90 mm Hg	Hyperbilirubinemia (total bilirubin >4 mg/dL [68 μmol/L])

Temp, temperature; HR, heart rate; RR, respiratory rate; WBC, white blood count; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

TREATMENT

- Goals of Treatment:** The primary goals include timely diagnosis and identification of the pathogen, prompt hemodynamic support, rapid identification of the pathogen and source control either medically and/or surgically, early initiation of appropriate intravenous antimicrobial therapy, and avoidance of complications such as organ failure and septic shock.
- Evidence-based treatment recommendations for sepsis and septic shock from the *Surviving Sepsis Campaign* are presented in **Table 43-2**.

TABLE 43-2

Evidence-Based Treatment Recommendations and Best Practice Statements

Recommendations	Recommendation Grades
Fluid Therapy	
Initial resuscitation from sepsis-associated hypotension with at least 30 mL/kg of IV crystalloid fluid within 1 hour	Strong recommendation, low evidence

Either balanced crystalloids or saline for additional fluids guided by frequent assessment of dynamic measures	Weak recommendation, low evidence
Antimicrobial Therapy	
IV broad-spectrum antibiotic within 1 hour of diagnosis of sepsis and septic shock against likely bacterial/fungal pathogens	Strong recommendation, moderate evidence
Empiric MRSA coverage for patients at high risk of MRSA	BPS
Reassess antibiotic therapy daily with microbiology and clinical data to narrow coverage (de-escalation)	BPS
Combination therapy for patients at high risk for multidrug-resistant bacterial pathogens	Weak recommendation, low-quality evidence
Optimize dosing strategies based on pharmacokinetics/pharmacodynamics parameters	BPS
Empiric antifungal therapy for patients at high risk of fungal infection	Weak recommendation, low evidence
Shorter duration of treatment duration using clinical evaluation and procalcitonin	Weak recommendation, low evidence
Vasopressors	
Initiate vasopressor therapy to maintain MAP ≥ 65 mm Hg	Strong recommendation, moderate evidence
Norepinephrine as the first-choice vasopressor	Strong recommendation, moderate evidence
Add vasopressin to norepinephrine instead of increasing norepinephrine dose to achieve adequate MAP	Weak recommendation, moderate evidence
Corticosteroids	
IV hydrocortisone for septic shock with ongoing requirement for vasopressor	Weak recommendation, low evidence
Hydrocortisone should be tapered when vasopressors are no longer required	Weak recommendation, low evidence
Glucose Control	
Use insulin dosing protocol when two consecutive blood glucose levels are >180 mg/dL (10 mmol/L), targeting an upper blood glucose <180 mg/dL (10 mmol/L)	Strong recommendation, high-level evidence
Venous Thromboembolism Prophylaxis	
Use daily low-molecular-weight heparin (LMWH) over unfractionated heparin	Strong recommendation, moderate evidence

Stress Ulcer Prophylaxis

Stress ulcer prophylaxis should be given to patients who have bleeding risk factors

Strong recommendation, low evidence

BPS, best practice statement; IV, intravenous; MAP, mean arterial pressure; MRSA, methicillin-resistant *S. aureus*.

ANTIMICROBIAL THERAPY

- Once the source of infection is identified, prompt efforts to eradicate that source should be made as progression of sepsis can occur despite rapid initial resuscitation, including fluid and appropriate antimicrobials in the absence of adequate source control.
- The Surviving Sepsis Campaign international guidelines recommend initiation of empiric broad-spectrum antibiotics with activity against likely pathogens and adequate concentration in the tissue presumed to be the source of infection within 1 hour of sepsis recognition.
- The selection of an optimal empiric regimen requires assessment of patient factors including age, concomitant underlying diseases, chronic organ dysfunction (ie, liver or renal failure), presence of immunosuppression (ie, active cancer, neutropenia, or uncontrolled HIV infection), or presence of indwelling devices (ie, central venous lines or urinary catheter).
- The antibiotics that may be used for empiric treatment of sepsis based on the site of infection and most likely pathogens are listed in [Table 43-3](#). While no specific empiric regimens are recommended in the guidelines, most institutions include **piperacillin/tazobactam**, **cefepime**, **meropenem** with or without **vancomycin**, or **linezolid** in the sepsis antibiotic guide. The guidelines generally suggest one gram-negative agent for empiric treatment for adults with sepsis or septic shock, as the combination therapy is not more effective than monotherapy in reducing organ failure or mortality in low-risk patients with sepsis without shock. Carbapenems remain the treatment of choice for serious infections due to extended-spectrum β -lactamase pathogens.
- For patients at high risk for sepsis or septic shock with MRSA, empiric antibiotic therapy with MRSA activity (**vancomycin**) should be combined with a broad-spectrum antibiotic.
- If *P. aeruginosa* is suspected, or with sepsis from hospital-acquired infections, an antipseudomonal cephalosporin (**ceftazidime** or **cefepime**), antipseudomonal fluoroquinolone (**ciprofloxacin** or **levofloxacin**), or an aminoglycoside should be included in the regimen.
- The average duration of antimicrobial therapy in a patient with sepsis is 7–10 days in the absence of source control issues, and fungal infections can require 14 days. The Surgical Infection Society recommends no more than 4 full days of antimicrobial therapy for patients with adequate source control and 8 days in critically ill patients in the intensive care unit (ICU) after achieving adequate source control.
- Preferred empiric therapy for suspected invasive candidiasis in nonneutropenic patients in the ICU is an echinocandin (**anidulafungin**, **micalafungin**, or **caspofungin**).
- Triazoles (**fluconazole**, **voriconazole**) are recommended in hemodynamically stable patients who have not had previous triazole exposure and not known to be colonized with azole-resistant *Candida* species.
- Empiric antimicrobial agents should be initiated immediately after the diagnosis of sepsis and septic shock is suspected due to the serious nature of the disease, but the antimicrobial regimen should be reassessed daily based on the microbiological and clinical data.

TABLE 43-3

Empiric Antimicrobial Regimens Based on Infection Source and Severity

Infection (Site or Type)	Antimicrobial Regimen		
	Community-Acquired, Immunocompetent	Healthcare-Associated and/or Immunocompromised	Additional Considerations
Undifferentiated	- Piperacillin/tazobactam - Cefepime - Meropenem	Meropenem	Vancomycin
Pneumonia	- Levofloxacin^a - Ceftriaxone + azithromycin	- Piperacillin/tazobactam - Meropenem^b - Cefepime^b Add levofloxacin or aminoglycoside^b	Vancomycin or linezolid
Intra-abdominal	- Ceftriaxone + metronidazole - Piperacillin/tazobactam - Ertapenem	- Meropenem - Piperacillin/tazobactam - Cefepime + metronidazole - Eravacycline	
Urinary tract	- Cefepime - Piperacillin/tazobactam - Ertapenem^c	- Piperacillin/tazobactam - Meropenem	Vancomycin
Skin/soft tissue	- Vancomycin - Linezolid - Daptomycin	Vancomycin + piperacillin/tazobactam	

^a Provided as 750 mg once daily.

^b If at risk for *P. aeruginosa*.

^c Risk for extended-spectrum β -lactamase producing pathogen.

FLUID AND HEMODYNAMIC SUPPORT

- Early effective fluid resuscitation is crucial for preventing further sepsis-induced tissue hypoperfusion or septic shock. The guidelines recommend administration with at least 30 mL/kg of IV crystalloid fluid given judiciously within the first 3 hours using ideal body weight. Target MAP is 65 mm Hg (8.6 kPa) to assess the need for vasopressors. Resolution of elevated serum lactate is desired to indicate adequate tissue perfusion and should be repeated within 2–4 hours of the initial elevated level.
- Fluid therapy guided by dynamic assessment of fluid responsiveness by examining cardiac output was associated with decreased mortality compared to standard care.

- Balanced crystalloids are recommended as first-line fluid for resuscitation based on cost and accessibility over colloid. Colloid (ie, albumin) can be used in patients who have already received considerable amount of crystalloids and continue to require fluid.
- [Hetastarch](#) products should be avoided at all times because they increased the risk of renal failure, need for renal replacement therapy, and death in multiple studies.
- Fluid therapy is based on the four phases of septic shock: ROSE—resuscitation, optimization, stabilization, and evacuation. **Resuscitation** phase occurs within minutes, and the patient will most likely have a positive fluid balance especially after the 30 mL/kg bolus. During the **Optimization** phase, within hours, the goal is to keep a neutral fluid balance between intake and output. During the **Stabilization** phase, which usually occurs in days, the focus should be on organ support and keeping fluid balance neutral to net negative with maintenance doses (30 mL/kg/day) of fluid only. Lastly, the **Evacuation** phase occurs in days to weeks, and it is suggested to keep fluid balance negative.

INOTROPE AND VASOACTIVE DRUG SUPPORT

- Vasopressors should be used with fluid therapy to achieve and maintain the MAP goal in septic shock and titrated carefully to an endpoint of adequate organ perfusion.
- Vasopressors should be used to achieve and maintain MAP goal of 65 mm Hg in fluid resuscitation–refractory shock, and they are titrated up carefully to an end point of adequate organ perfusion. Selection and dosage are based on the pharmacologic properties of various catecholamines and how they influence hemodynamic parameters ([Table 43-4](#)).
- For septic patients with clinical signs of shock and significant hypotension unresponsive to aggressive fluid therapy, norepinephrine is the first-line agent for patients with septic shock. In comparison to dopamine, it is less arrhythmogenic and was associated with lower risk of mortality. Dopamine may be considered as an alternative agent to norepinephrine in a small subset of patients who have bradycardia or are at low risk of developing arrhythmia.

TABLE 43-4

Mechanism of Action and Hemodynamic Effects of Vasopressors in Septic Shock

Drug	Receptor Affinity				Physiologic Outcome			
	Dopamine	Alpha-1	Beta-1	Beta-2	HR	SV	SVR	CO
Dobutamine (2–10) ^a	--	+	++++	++	↑	↑	↔ or ↓	↑↑
Dobutamine (>10–20) ^a	--	++	++++	+++	↑	↑	↔ or ↓	↑↑
Dopamine (0.5–2) ^a	+++	–	+	–	↔↑	↑	↔ or ↑	↑
Dopamine (5–10) ^a	++	+	+++	+	↑	↑	↔ or ↑	↑↑
Dopamine (10–20) ^a	++	+++	++	–	↑	↑	↑↑	↑
Epinephrine (0.01–0.05) ^a	–	++	++++	+++	↑	↑	↑↑	↑
Epinephrine (0.05–0.3) ^a	--	++++	+++	+	↑	↑	↑↑	↑↑
Norepinephrine (0.02–3) ^a	–	++++	++	+	↔ or ↑	↔	↑↑	↑
Phenylephrine (0.5–9) ^a	–	+++	–	–	↔ or ↓	–	↑↑	↔
Vasopressin (0.01–0.03) ^b	V1 and V2 receptors				↔ or ↓	–	↑↑	↔ or ↓
Angiotensin II (1.25–80) ^c	AT-1 receptor				↑	–	↑	↑

^aMeasured in mcg/kg/min.

^bMeasured in units/min.

^cMeasured in ng/kg/min.

CO, cardiac output; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance; V1, vasopressin receptor 1; V2, vasopressin receptor 2.

PERFORMANCE IMPROVEMENT BUNDLE

- The Surviving Sepsis Campaign recommends implementation of hospital-based performance improvement efforts such as a core set of recommendations (“bundle”) to improve patient outcomes ([Table 43-5](#)).

TABLE 43-5

Surviving Sepsis Campaign Performance Improvement Bundle of Care

One-Hour Bundle

- Measure initial **lactate**
- Repeat in 2 hours if initial **lactate** >18 mg/dL (>2 mmol/L)
- Obtain cultures (blood, urine, sputum, etc) prior to administration of antibiotics
- Administer broad-spectrum IV antibiotics within 1 hour
- Initial fluid resuscitation of 30 mL/kg crystalloid for hypotension or **lactate** >36 mg/dL (≥4 mmol/L)
- Vasopressors if MAP <65 mm Hg during or after completion of fluid resuscitation

IV, intravenous; MAP, mean arterial pressure.

ADJUNCTIVE THERAPY

- Initiate insulin therapy at a glucose level of greater than 180 mg/dL (10 mmol/L), with a target range between 144 and 180 mg/dL (8–10 mmol/L).
- Add low-dose **hydrocortisone** 200 mg/day for patients with septic shock who require ongoing norepinephrine dose of >0.25 mcg/kg/min at least 4 hours to maintain the target MAP. **Hydrocortisone** should be tapered when vasopressors are no longer required because hemodynamic and immunologic rebound effects have been reported with abrupt cessation of corticosteroids.
- Venous thromboembolism prophylaxis with daily subcutaneous **low-molecular-weight heparin** should be initiated in patients with sepsis and septic shock. If pharmacologic prophylaxis is contraindicated, mechanical prophylactic measures should be considered.
- Stress ulcer prophylaxis should be initiated in all patients with sepsis and septic shock who have risk factors for GI bleeding.

See [Chapter 147](#), *Sepsis and Septic Shock*, authored by S. Lena Kang-Birken, Sul R. Jung, and Caroline L. Ko for a more detailed discussion of this topic.